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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/963,693	09/25/2001	Gary Ruvkun	00786/351006	2040

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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 08/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/963,693	RUVKUN ET AL.	
	Examin r	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *4-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-6* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-6 are pending.

▷ *Applicants are advised to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). Each amendment document that includes a change to an existing claim, or submission of a new claim,* ***must include a complete listing of all claims*** *in the application. After each claim number, the status must be indicated in a parenthetical expression, and the text of each claim under examination (with markings to show current changes) must be presented. The listing will serve to replace all prior versions of the claims in the application.*

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In instant case the PCT/US98/10080, US 08/888,534 and 08/857,076 does not disclose the subject matter as claimed in the instant application. These priority documents do not disclose the PTEN and its use to evaluate impaired glucose tolerance condition obesity or longevity in a sample by measuring PTEN lipid phosphatase activity.

Accordingly the priority date of instant application is 12/03/98 on which the parent application U.S. 09/205,658 was filed.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-3, drawn to a method of diagnosing an impaired glucose tolerance condition obesity or longevity in a patient by analyzing the level of PTEN expression or activity in a sample by measuring PTEN lipid phosphatase activity, classified in class 435, subclass 4.

II. Claims 4 and 6, drawn to a method of ameliorating or delaying the onset of an impaired glucose tolerance condition in a patient by administering a compound that decrease PTEN expression or activity classified in class 514, subclass 2.

III. Claims 5 and 6, drawn to a method of increasing longevity in a patient by administering to the patient PTEN polypeptide or a compound that increase PTEN expression or activity, classified in class 514, subclass 2.

The inventions are distinct, each from the other because of the following reasons:

Inventions I is distinct from inventions II and III. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the method of evaluating PTEN expression or activity has different modes of operation, function and effects as compared to the method of treatment of impaired glucose tolerance condition by administering a compound that decrease PTEN expression or activity. Invention I requires the evaluation of PTEN expression or activity in vitro, where as inventions II and III requires in-vivo administration of therapeutic compounds. Thus these inventions are distinct and are of separate uses.

Inventions II and III are distinct. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different

functions, or different effects (MPEP § 806.04, MPEP § 808.01). In instant case impaired glucose tolerance different modes of functions and effects as compared to extension of life span. For example impaired glucose tolerance conditions involves insulin related cellular functions, whereas increase in longevity depends upon non-insulin related cellular functions. Thus these inventions are distinct and are of separate uses.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Karen Elbing on 5/20/03 a provisional election was made without traverse to prosecute the invention of **Group I, claims 1-3**. Affirmation of this election must be made by applicant in replying to this Office action. Claims 4-6 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Myers et al (PNAS 94:9052-9057, 1997). Myers teaches that PTEN is a tumor suppressor gene identified on chromosome 10. The cited art further teaches that PTEN, which is located on locus 10q22-23 is deleted or mutated in a significant fraction of glioblastomas and prostrate tumors. The cited art further teaches that germ line mutation in PTEN gene give rise to Cowden disease which is associated with the formation of multiple benign tumors and increases susceptibility to malignant cancers (page 9052, col.1-2). The cited art further teaches phosphatase assays to evaluate PTEN activity (page 9053 col.2 para 2). The cited art further teaches evaluation of PTEN related phosphatase activity in various PTEN mutants (page 9055, col.1 para 2; page 9056, fig-4, fig-5). The cited art further teaches that a point mutation discovered in a glioma sample that changes Leu57-Trp (L57W) eliminates PTEN phosphatase activity (page 9056, col.2 para.2). The cited art further teaches that loss of PTEN activity leads to progression of cells to a cancerous state. The cited art further establishes a correlation between the severity in the disruption of PTEN activity and the pathology[1] of diseases (The scientific study of the nature of disease and its causes, processes, development, and consequences) like Bannayan-Zonana and Cowden disease (page 9057,

col.1 para.3). Given the broadest reasonable interpretation the development of a cancer or tumors has inherently been associated with decreased longevity in a patient. Thus the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Myers et al (PNAS 94:9052-9057, 1997 as applied to claim 2 above, and further in view of Maehama et al (J Biol. Chem. 237(22):13375-13378, 1998)

Myers teaches that PTEN is a tumor suppressor gene identified on chromosome 10. The cited art further teaches that PTEN, which is located on locus 10q22-23 is deleted or mutated in a significant fraction of glioblastomas and prostrate tumors. The cited art further teaches that germ line mutation in PTEN gene give rise to Cowden disease which is associated with the formation of multiple benign tumors and increases susceptibility to malignant cancers (page 9052, col.1-2). The cited art further teaches phosphatase assays to evaluate PTEN activity (page 9053 col.2 para 2). The cited art further teaches evaluation of PTEN related phosphatase activity in various

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[1] *The American Heritage® Dictionary of the English Language, Third Edition* copyright © 1992 by Houghton Mifflin Company. Electronic version licensed from INSO Corporation; further reproduction and distribution restricted in accordance with the Copyright Law of the United States. All rights reserved.

PTEN mutants (page 9055, col.1 para 2; page 9056, fig-4, fig-5). The cited art further teaches that a point mutation discovered in a glioma sample that changes Leu57-Trp (L57W) eliminates PTEN phosphatase activity (page 9056, col.2 para.2). The cited art further teaches that loss of PTEN activity leads to progression of cells to a cancerous state. The cited art further establishes a correlation between the severity in the disruption of PTEN activity and the pathology[2] of diseases (The scientific study of the nature of disease and its causes, processes, development, and consequences) like Bannayan-Zonana and Cowden disease (page 9057, col.1 para.3). Given the broadest reasonable interpretation the development of a cancer ot tumors has inherently been associated with decreased longevity in a patient. However, Myers does not teach evaluation of expression or activity of PTEN by analyzing a lipid phospatase activity.

Maehama teaches the tumor suppressor, PTEN/MMAC1, dephosphorylates the lipid second messenger, phosphatidylinositol 3,4,5-trisphosphate (PtdIns(3,4,5)P_3). The cited art further teaches that PtdIns(3,4,5)P_3 is a key molecule involved in cell growth signaling. The cited art teaches that the PTEN catalyzed dephosphorylation of PtdIns(3,4,5)P_3, specifically at position 3 on the inositol ring. (see abstract). The cited art further teaches that PTEN has tumor suppressive activity (col.1 para.1). The cited art further teaches further teaches a method of determining PtdIns(3,4,5)P_3 in a biological sample comprising human 293cells (Page 13375, col.2 para.3). In addition the cited art further teaches a method of determining PI 3-kinase activity (Page 13375, col.2 para.4

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the method as taught by Myers by substituting the substrate of PTEN with

PtdIns(3,4,5)P_3. One would have been motivated to do so because PTEN has been known to encode the active site consensus motif HCXXGXR(S/T) found in all (protein-tyrosine phosphatases (PTPases) that elicits phosphoinositide phosphatase activity. One would have a reasonable expectation of success since PTEN has been known to catalyze the dephosphorylation of PtdIns(3,4,5)P_3 specifically through position 3 on the inositol ring. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention:

Invention relates to a method of diagnosing **impaired glucose tolerance condition** and **obesity** in a patient.

Breadth Of Claims And Guidance Provided By The Inventor:

The instant claims are drawn to a method of diagnosing impaired glucose tolerance condition, obesity and longevity in a patient by analyzing the level of PTEN expression or

activity in a sample isolated from patient by measuring PTEN related any and all lipid phosphatase activity. The specification teaches Daf-18 maps to a genetic region which bears the probable C. elegans homologue (T07A9.6) of the tumor suppressor gene PTEN. Consistent with the role of PTEN as a daf-18 homologue is the fact that PTEN has lipid phosphatase activity that dephosphorylates position 3 on the inositol ring of PIP3 in vitro and decreases the levels of the lipid products of PI3K in response to insulin signaling in human 293 cells. The applicant hypothesized that a decrease in PTEN activity would be predicted to enhance PI3K signaling, consistent with daf-18 activity (spec. page 108, lines 9-22). At best the specification only disclosed a C.elegans model wherein the interaction of various daf-proteins in the regulation of glucose metabolism and longevity has been studied (spec pages 108-117). The specification further disclosed that PTEN and C.elegans daf-18 have very limited sequence similarity (spec. fig-39B). The specification further hypothesized that PTEN on chromosome 10 is a candidate gene for human autosomal dominant type II diabetes as well as for human longevity control. Reduction in PTEN activity would be expected to potentiate insulin and/or insulin-like growth factor signaling, but an increase of PTEN activity would be expected to cause insulin resistance downstream of the insulin receptor, the type observed in late onset diabetes. However the specification as failed to establish the role of PTEN in mammalian glucose homeostasis.

State Of Art And Predictability:

The state of the art at the time of filing teaches that the development of impaired glucose tolerance and obesity is multi-factorial and complex. Obesity and type 2 diabetes are the most prevalent and serious metabolic diseases that are associated with a chronic inflammatory response characterized by abnormal cytokine production, increased acute-phase reactants and

other stress-induced molecules. Many of these alterations seem to be initiated and to reside within adipose tissue, an unusual site for inflammation. Elevated production of tumour necrosis factor (TNF)-α by adipose tissue decreases sensitivity to insulin and has been detected in several experimental obesity models and obese humans. Free fatty acids (FFAs) are also implicated in the etiology of obesity-induced insulin resistance, although the molecular pathways involved in their action remain unclear (Hirosumi et al. Nature.420(6913):333-6 2002). Even though activation of PI3K is necessary for full stimulation of glucose transport by insulin, emerging evidence suggests that it is not sufficient and another pathway may also be necessary. The signals downstream of PI3K are still unknown, and there is controversy as to whether the serine/threonine kinase Akt/protein kinase B (PKB) or the protein kinase C (PKC) isoform λ/ζ mediates insulin stimulation of glucose transport. The pathways that mediate insulin's metabolic effects diverge downstream of PI3K and show differential sensitivity to varying levels of insulin (Khan et al. J. Clin. Invest. 106(4):473-481, 2000 page 473, col.2, page 475, fig-1). Furthermore, insulin resistance in obesity and type 2 diabetes is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output caused by downregulation of the major insulin-responsive glucose transporter, GLUT4 (Khan page 474 co.1, para.1). In addition FFA, leptin and TNF-α are other likely candidates that are know to affect glucose homeostasis (Khan page 474 col.2, page 476 fig-2). Furthermore, under hyperglycemic, hyperinsulinemic conditions, muscle glycogen synthesis is the major pathway for glucose metabolism in both normal and diabetic individuals, wherein the defective muscle glycogen synthesis plays a major role in causing insulin resistance in patients with type 2 diabetes. Defects in glycogen synthase, hexokinase II,

and glucose transport have also been implicated in the loss of muscle glycogen synthesis in type 2 diabetics. In addition increased plasma free fatty acid concentrations are typically associated with many insulin-resistant states, including obesity and type-2 diabetes mellitus (Shulman J Clin. Invest. 106:171-176, 2000, see page 171 col.2 para.2, page 172 col.2 para.3; fig-2). In addition, obesity is a complex phenotype which is not only the result of genetic variations but is also the out come of personal behavioral and life style (Lonnqvist et al Nat. Med. 1(9):950-953, 1995, see page 951 col.1 para.1 line 1). Obesity appears to lessen life expectance markedly especially among young adults (Fontaine et al JAMA 289:187-193, 2003). Therefore considering the applicant's disclosure it is even unclear how one skill in the art would conclude that increase in PTEN activity that causes obesity would not leads to decreased longevity or visa versa (especially in context of invention as claimed in claim 2). The state of the art a the time of filing was such that it has been unclear whether the PTEN (daf-18) activity is regulated during insulin-like signaling or any other signaling activity, since PTEN lipid phosphatase activity is low in vitro due to a missing modification by the insulin signaling cascade (Ogg et al, Mol Cell 2:887-893, 1998). Since the factors that affect PTEN activity in vivo are not well understood it is unclear what would be a representative control sample that can be used to evaluate the claimed PTEN activity. In addition it is unclear how one skill in the art would diagnose impaired glucose tolerance condition or propensity thereto by analyzing PTEN lipid phosphates activity alone in type-I diabetic patients, wherein the impaired glucose tolerance is the result of loss of insulin secretion. Thus considering the limited amount of guidance provided in the specification as filed and the state of art at the time of filing one skill in the art would have to engage in excessive and undue amount of experimentation to establish role of PTEN in glucose homeostasis.

Quantity Of Experimentation Required:

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson , 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case the specification as failed to establish the role of PTEN in mammalian glucose homeostasis and/or obesity. Diagnosis of impaired glucose tolerance condition and obesity by analyzing any and all kind of PTEN lipid phosphatase activity in any and all tissues sample is not considered routine in the art and without sufficient guidance to role or PTEN in glucose homeostasis and/or obesity, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the unpredictability in the art and the limited guidance provided in the specification as filed one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation required would include scientific evaluation of the role of

PTEN in impaired glucose tolerance and obesity especially in context with the multi factorial nature of these disorders.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sumesh Kaushal.

SUMESH KAUSHAL
PATENT EXAMINER